

# **Per-oral Pancreatoscopy-guided Lithotripsy vs. Extracorporeal Shock Wave Lithotripsy For Treating Symptomatic Main Pancreatic Duct Stones in Chronic Pancreatitis: A Multicenter Randomized Clinical Trial**

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## Synopsis

<b>Title</b>	<b>Per-oral Pancreatotomy-guided Lithotripsy vs. Extracorporeal Shock Wave Lithotripsy in Chronic Pancreatitis: A Multicenter Randomized Clinical Trial</b>
<b>Investigators</b>	<ul style="list-style-type: none"> <li>• Raj J. Shah, University of Colorado (Principal Investigator)</li> <li>• Samuel Han, University of Colorado (Principal Investigator)</li> <li>• Vikesh Singh, Johns Hopkins University</li> <li>• Isaac Rajjman, Baylor St. Luke's Medical Center</li> <li>• Michel Kahaleh, Rutgers Robert Wood Johnson Medical Center</li> <li>• Paul Tarnasky, Methodist Dallas Medical Center</li> <li>• Martin Freeman, University of Minnesota</li> </ul>
<b>Hypothesis</b>	<ul style="list-style-type: none"> <li>• The <u><b>central hypothesis</b></u> is that per-oral pancreatoscopy-guided lithotripsy is superior to extracorporeal shock wave lithotripsy in clearance of refractory main pancreatic duct stones, thereby improving pain levels and quality of life in patients with chronic calcific pancreatitis.</li> </ul>
<b>Primary Objective</b>	<ul style="list-style-type: none"> <li>• To demonstrate the superiority of per-oral pancreatoscopy over extracorporeal shock wave lithotripsy in clearance of refractory main pancreatic duct stones in patients with chronic pancreatitis. Failure to remove any or all stones with the initial intervention will be an outcome recorded for the study.</li> </ul>
<b>Secondary Objective</b>	<ul style="list-style-type: none"> <li>• To demonstrate the effect of stone clearance to reduce pain and opiate use and improve quality of life.</li> </ul>
<b>Time Line</b>	<ul style="list-style-type: none"> <li>• Enrollment will be performed over a 24-month time period with follow-up performed at 1, 3, 6, and 12 months after ductal clearance.</li> </ul>
<b>Primary Endpoint</b>	<ul style="list-style-type: none"> <li>• Main pancreatic duct stone complete clearance rate</li> </ul>
<b>Secondary Endpoints</b>	<ul style="list-style-type: none"> <li>• Change in quality of life</li> <li>• Change in pain scores</li> <li>• Change in opiate use</li> <li>• Number of procedures</li> <li>• Adverse Events related to therapies</li> </ul>
<b>Study Design</b>	<ul style="list-style-type: none"> <li>• Multicenter randomized trial</li> </ul>
<b>Sample Size</b>	<ul style="list-style-type: none"> <li>• 150 patients</li> </ul>

## **List of Abbreviations**

PD: pancreatic duct

PPL: per oral pancreatoscopy-guided lithotripsy

ESWL: extracorporeal shock-wave lithotripsy

EHL: electrohydraulic lithotripsy

LL: laser lithotripsy

ERP: endoscopic retrograde pancreatography

ERCP: endoscopic retrograde cholangiopancreatography

AE: adverse event

EUS: endoscopic ultrasound

CT: computed tomography

MRCP: magnetic resonance cholangiopancreatography

## STUDY PROTOCOL

### **1.1 Research Questions and Hypothesis**

Pain relief poses a significant challenge in patients with chronic pancreatitis given the paucity of effective medications and interventions. Approximately 50-90% of patients with chronic pancreatitis develop pancreatic duct (PD) stones which can obstruct the PD, causing ductal hypertension that can lead to severe pain.<sup>1</sup> This pain is frequently treated with opiates, which not only pose a risk of addiction but are also associated with increased hospitalization rates.<sup>2</sup> Traditional methods to remove PD stones include endoscopic retrograde pancreatography (ERP) with sphincterotomy, stricture dilation, and balloon or basket extraction and extracorporeal shock-wave lithotripsy (ESWL) for larger stones.<sup>3,4</sup> A potential benefit of ERP techniques over ESWL alone is the ability to treat underlying pancreatic duct strictures with therapeutic PD stenting to not only facilitate stone removal but potentially to help reduce stone recurrence by improving pancreatic juice flow.<sup>5,6</sup> As shown previously, use of ESWL alone without treatment of strictures is associated with a significantly higher stone recurrence rate.<sup>7</sup> Furthermore, ESWL does not remove stone fragments and ERP techniques are required for this aspect of stone clearance.<sup>8</sup> If ERP with PPL is performed it may obviate the need for ESWL except in special circumstance such as significantly impacted pancreatic stone burden in the head of the pancreas. These methods, however, may be limited by imprecision, limited ESWL availability for PD stone therapy in the US, requirement of multiple treatment sessions, and decreased efficacy in removing larger, impacted stones.<sup>9,10</sup> From a practical standpoint, the need to frequently outsource ESWL to urologists limits the ability of gastroenterologists to control the timing of these sessions and assess efficacy while potentially increasing patient costs, time commitment, and use of general anesthesia. If ineffective in stone clearance, surgery remains a last-resort option that is associated with high morbidity (18-53%) and mortality (0-4.55%).<sup>11</sup> The introduction of per oral pancreatoscopy, or direct endoscopic visualization of the PD, has enabled targeted intraductal therapy, including electrohydraulic lithotripsy (EHL) and laser lithotripsy (LL) for these refractory stones.<sup>12</sup> None of these treatment methods have been studied in prospective trials and there is a lack of comparative data between ERCP techniques and ESWL in removing stones, whether they improve pain and quality of life, and reduce opiate use along with assessing financial costs. There is, therefore, a *critical need* to compare the efficacy of per oral pancreatoscopy-guided lithotripsy (PPL) with ESWL and determine which therapy provides better outcomes with a goal of less procedures and that is more cost-effective in removing difficult PD stones. Without such information, the treatment of main pancreatic duct stones associated with chronic pancreatitis will likely remain limited anecdotal and consisting of retrospective case series.

Our *long-term goal* is to determine the optimal treatment regimen for chronic pancreatitis-related pain associated with main pancreatic duct stones. Our *overall objectives* in this application, which is the next step toward attainment of our long-term goal, are to (i) determine whether PPL is superior to ESWL in removing main pancreatic duct stones, and (ii) ascertain the effectiveness

of PPL or ESWL in improving pain and quality of life. Our central hypothesis is that PPL is superior to ESWL in removing difficult PD stones, thereby improving pain levels and quality of life in patients with chronic calcific pancreatitis. Our hypothesis has been formulated based on previous retrospective studies from our group demonstrating a higher stone clearance rate with PPL compared to published stone clearance rates for ESWL.<sup>6,13,14</sup> The rationale for this project is that the determination of the superior lithotripsy method and its effect on pain and quality of life is likely to guide clinical decision-making in patients with PD stones whereby optimal strategies for the treatment of chronic pancreatitis can be developed. To attain the overall objective, the following two specific aims will be pursued:

1. **Perform a multicenter randomized clinical trial to compare the efficacy of per oral pancreatoscopy-guided lithotripsy with extracorporeal shock-wave lithotripsy in the removal of refractory pancreatic duct stones.** Based on preliminary data, our working hypothesis is that PPL is superior to ESWL in the clearance of PD stones.
2. **Compare the effect of per oral pancreatoscopy-guided lithotripsy with extracorporeal shock-wave lithotripsy in reducing pain and improving quality of life in patients with chronic pancreatitis.** Based on preliminary data, our working hypothesis is that stone clearance will reduce pain levels, decrease opiate use, and improve quality of life.

At the completion of the proposed research, our expected outcomes are to have determined which lithotripsy method is clinically superior in PD stone removal. We also expect to demonstrate the effect of PD stone removal on pain and quality of life. These results are expected to have an important positive impact because they will provide a strong evidence-based support for endoscopic therapies to ultimately treat chronic calcific pancreatitis more effectively.

## **1.2 Basic Design of the Study**

This study is a multicenter randomized trial comparing per oral pancreatoscopy-guided lithotripsy (PPL) using either laser lithotripsy (LL) or electrohydraulic lithotripsy (EHL) with extracorporeal shock wave lithotripsy (ESWL) in removing main pancreatic duct (PD) stones from patients with chronic calcific pancreatitis.

Specific aims for this trial include:

- **SA1:** To determine whether PPL is more effective than ESWL in removing refractory PD stones in terms of main pancreatic duct stone clearance rate in patients with chronic calcific pancreatitis who have stones refractory to standard therapy.
- **SA2:** Evaluate the effectiveness of main pancreatic duct stone removal in reducing pain and improving quality of life in patients with chronic calcific pancreatitis.
  - **SA2a:** To determine whether a greater clearance of PD stones via PPL or ESWL will improve quality of life to a greater extent.

- **SA2b:** To determine whether a greater clearance of PD stones via PPL or ESWL will reduce pain and opiate requirements to a larger extent.

The primary endpoint of this trial will be complete clearance of main PD stones in eligible patients. This study will be statistically powered to detect superiority of PPL over ESWL in this primary endpoint. Major secondary endpoints will include: 1) change in quality of life after PD stone removal; 2) change in pain levels after PD stone removal; 3) change in opiate use after PD stone removal; 4) comparison of total number of procedures in both arms, and 5) PD stone recurrence rate .

### **Sample and Methodology**

We will enroll 150 subjects (**Figure 1**) with chronic pancreatitis who have symptomatic main PD stones identified by non-invasive imaging or endoscopic ultrasound that are refractory to standard endoscopic retrograde pancreatography (**ERP**) techniques.

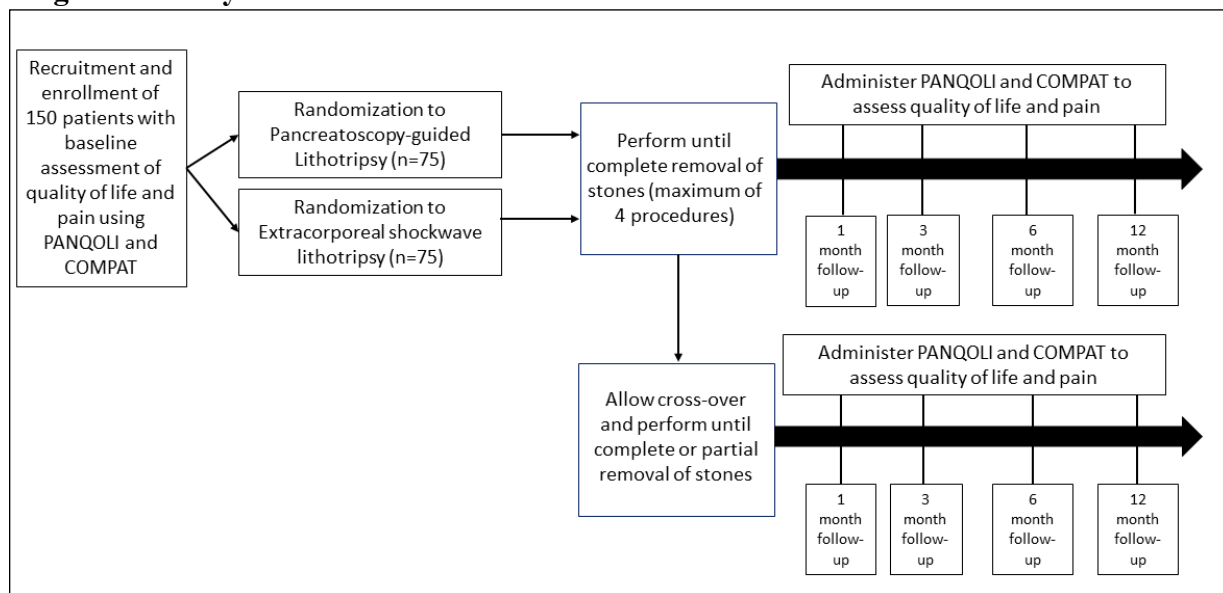
Following baseline assessments and identification of main PD stones refractory to conventional ERP techniques, patients will be randomly assigned to receive either PPL or ESWL as the primary lithotripsy method to fracture PD stones. Both these procedures represent potential next steps in the algorithm of managing PD stones.<sup>3</sup> If partial clearance (removal of some, but not all stones) of PD stones is achieved as determined by the performing endoscopist, subjects can receive repeated PPL or ESWL sessions (for a maximum of 4 sessions total as is commonly practiced before referral for alternative therapy) until complete removal of stones is achieved.<sup>5</sup> Failure to remove any main PD stones will be considered a failure of the treatment. Additionally, failure to achieve complete clearance within a maximum of 4 sessions of either PGL or ESWL will be considered a treatment failure even if partial clearance is achieved.

Cross-over and/or combination therapy will be allowed at the discretion of the endoscopist after treatment failure. As described in the statistical analysis, under the intention-to-treat (primary) analysis, should cross-over occur, the final outcome of complete stone clearance will be attributed to the initial therapy. Under the per-protocol (secondary) analysis, in the case of cross-over, the final outcome of complete stone clearance will be attributed to the combination of ESWL and PPL. Similarly, in terms of survey collection, should cross-over occur, the analysis of the survey results will be attributed to the originally assigned intervention in the intention-to-treat (primary) analysis. In the per-protocol (secondary) analysis, the outcomes will be attributed to the combination of both interventions resulting in technical success.

Stone clearance will be determined by either pancreatography (via ERCP or MRCP) or EUS showing the absence of main PD stones. Complete stone clearance will be defined as the absence of stones in the head or body of the main PD. Partial stone clearance will be defined as the removal of more than 50% but less than 100% of stone/stone fragments in the head or body of the main PD.

Following complete PD stone removal, patients will be given a validated quality of life instrument, the PANQOLI at 1, 3, 6, and 12 months post-treatment. Similarly, the comprehensive pain assessment tool (COMPAT) will also be given at 1, 3, 6, and 12 months post-treatment. Lastly, daily opiate use will be recorded at 1, 3, 6, and 12 months post-treatment.

**Figure 1: Study Flowsheet**



### **1.3 Subject Inclusion and Exclusion Criteria**

#### **Inclusion Criteria:**

- Subjects with abdominal pain secondary to chronic calcific pancreatitis and main pancreatic duct stones found on cross-sectional imaging, EUS, or ERP.
- Subjects aged 18-80.
- Subjects must have failed at least one prior attempt of standard ERP to remove the PD stones.
- Main PD stones in the head or body that are greater than 50% of the immediate downstream diameter of the pancreatic duct.
- Stones  $\geq 5$  mm in diameter or impacted in the main PD on cross-sectional imaging or EUS. If multiple locations of stones are noted within the main PD, pancreatic tail stones cannot comprise more than one-third of the stone burden within the main PD.

#### **Exclusion Criteria:**

- Subjects who have previously received PPL or ESWL.

- Patients with PD stones isolated in the tail or side branches of the main duct.
- Inability to place a transpapillary pancreatic duct stent at index ERP.
- Patients with prior pancreatic surgery
- Pancreas divisum or acquired pancreas divisum requiring minor papilla cannulation
- Pregnancy
- Significant cardiopulmonary co-morbidities precluding general anesthesia
- Patients with implanted cardiac pacemakers or defibrillators
- Patients with coagulation disorders that cannot be corrected to an INR below 2.0
- Patients with ongoing alcohol and/or illicit drug use

### **Screening/Baseline Evaluation**

Potential eligible patients will undergo an initial visit in which eligibility will be confirmed and the trial protocol explained in detail. All willing and eligible patients providing informed consent will have baseline data obtained including detailed history of chronic pancreatitis (i.e. disease duration, etiology, drug use, and family history of pancreatic disease), endoscopy history, and current medication use. Baseline quality of life and pain levels will also be obtained.

### **Randomization**

Randomization will occur after informed consent is obtained and prior to receiving lithotripsy. Once the patient has received an ERP which failed to completely remove PD stone(s)  $\geq 5$  mm with the largest stone diameter greater than 50% the diameter of the downstream PD and a transpapillary pancreatic duct stent has been inserted, a white envelope will be opened by a research coordinator, informing the patient and investigator which lithotripsy therapy will be subsequently performed. Attempt at pancreatic duct stenting beyond or to the level of the most downstream main pancreatic duct stone will be made prior to procedure completion. Randomization will be performed using a 1:1 ratio.

### **Treatment Regimens**

#### *Per oral pancreatoscopy-guided lithotripsy*

Standard ERP will be performed to cannulate the PD, perform pancreatic sphincterotomy, and stricture dilation as necessary. A pancreatoscope (Spyglass Digital System, Boston Scientific, Marlborough, MA) will then be inserted through the duodenoscope into the PD. For PPL, electrical pulses will be delivered through an aqueous medium by EHL or LL with the probe tip in contact with or 1-2mm away from the stone. Settings for EHL (1.9F fiber; Autolith, Northgate Technologies, Elgin, IL) are 10-20 pulses/second with a power of 50-100; and for LL (200, 272, or 365 micrometer fiber, Versa Pulse Power Suite 20-W Holmium laser, New Star, Roseville, CA) ranging from 0.8 – 2.5 Joules with a frequency of 8-15Hz and power of 9-30 W. A maximum of 1 hour of intraductal lithotripsy will be allowed to reduce performance bias.



#### *Extracorporeal shock wave lithotripsy*

Stone localization will first be performed by obtaining high-quality plain films of the pancreatic area in left and right oblique positions using a two-dimensional radiologic targeting system. Depending on the stone localization, ESWL will then be performed with the patient in either slight left or right lateral decubitus with shock waves entering the body from the ventral side. The shockwaves will be focused first on the most distally located stone within the main duct and then on other calculi moving from the head towards the body. If a stent has been inserted during preceding ERP then this may also serve as a guide to target main pancreatic duct stones by ESWL. A total of one hour of ESWL at a rate of 60-120 shocks/minute will be delivered in one treatment session.

### **1.4 Standard of Care/Research Procedure**

The current standard of care for the treatment of PD stones varies by region. In Europe, extracorporeal shock-wave lithotripsy (**ESWL**) is a primary method by which stones are fragmented. Once ESWL is performed, however, ERP is still performed to remove the stone fragments. In Europe, ESWL is frequently performed by gastroenterologists who can perform ERP as well.

In the United States, however, ESWL is primarily performed by urologists for the treatment of kidney stones. Few gastroenterologists have direct access to ESWL and urologists remain hesitant to use ESWL for non-kidney stones. Therefore, in the United States, standard therapy has become ERP.<sup>4</sup> In ERP, pancreatography is performed by cannulating the PD and then injecting radio-opaque iodine contrast into the PD. Pancreatography allows for radiographic visualization of a stone and associated strictures; stone removal can be achieved by sweeping the PD with either a balloon or basket after performing a pancreatic sphincterotomy where the sphincter opening the PD is cut and coagulated. This is often followed by balloon or catheter dilation of any downstream pancreatic duct strictures. ERP is typically made more difficult by strictures downstream of the stones and the presence of numerous, large (>5mm in diameter) or hard stones.

In this study, PPL will be compared with ESWL. Pancreatoscopy, the placement of a small endoscope directly into the PD, allows for direct visualization of the PD and stones. This allows for intraductal lithotripsy to be performed while directly visualizing the stones. Briefly, EHL, one version of intraductal lithotripsy, creates high-frequency shock-wave pulses which generate energy that can result in the fragmentation of stones. LL, on the other hand, involves the focusing of laser light on the surface of a stone which can induce wave-mediated stone fragmentation. Both techniques can fragment stones into smaller pieces, which can then be swept out of the PD using standard techniques such as balloon or basket sweeping.

Upon completion of the procedure, all patients will be observed in the post-anesthesia care unit for 1 hour as is the current standard of care. Following the index ERP session and sphincterotomy, extended recovery in the hospital or discharge will be planned per institutional practice. If patients exhibit symptoms such as intractable abdominal pain or severe N/V, they will be admitted for overnight observation. All patients will receive a phone call within 48 hours of discharge as is standard practice to identify any short-term AE's.

### **1.5 Subject and Study Stopping Criteria**

Subjects may withdraw from the study at any time for any reason. Subjects can also be withdrawn from the study at any time at the discretion of the investigators for breach of study protocol or emergence of an exclusion criteria (i.e. pregnancy).

The study can be stopped at any point should the Data Safety Monitoring Board (DSMB) request cessation of the trial based on any compilation of adverse events or clear demonstration of superiority of one technique. Similarly, should the interim analysis reveal futility in that the study hypothesis is deemed unprovable within the constraints of the study, the study may be stopped. The study will also be stopped once the intended sample size goal is reached and 6-month follow-up has been obtained. Lastly, the study can be stopped should study costs exceed the allotted budget.

### **1.6 Data Collection Tool**

A comprehensive system has been previously developed at this institution, and will support the data collection and reporting needs of this project which includes: (i) streamlining data collection from the participating centers, (ii) creating a secure database from which statistical analysis can be performed. Data will be stored at the University of Colorado instance of REDCap<sup>15</sup>, which resides on a local secure server. Data regarding stone clearance rates and adverse events will be entered by investigators at each center. Using an Application Programming Interface (API), data can be transferred to and from REDCap to SAS software (v.9.3, SAS Institute, Cary, NC) used to export data from REDCap to SAS to conduct analysis. SAS software interfaces seamlessly with REDCap-produced syntax files (i.e. SAS code) and SAS-ready CSV (comma separated variables) data files. Results of these analyses will be imported back into REDCap, using the API, for long-term storage, reference, and further analysis. Access to these data will be controlled by a custom module and all users of the site will be required to log in. No protected health information will be collected or displayed and data stored in our HIPAA compliant server environment to ensure privacy.

### **1.7 Data Analysis Plan**

Statistical Analysis: Comparison of technical success rate, defined as the rate of complete clearance of PD stones, between PPL and ESWL will be performing using the chi-squared test or Fisher's exact test. Secondary outcomes including adverse event (both overall and serious

adverse event) rates, procedure length, and number of procedures will be compared using a chi-square test or Fisher's exact test for categorical variables and the Student's t test will for continuous variables. A p value  $<0.05$  will be considered significant. In the primary analysis, all results will be analyzed under an intention-to-treat protocol. A per-protocol (secondary) analysis will also be performed where the technical success will be attributed to the combination of modalities resulting in achieving the primary outcome should cross-over occur.

To identify predictors for technical success, a multivariable logistic regression will be performed incorporating variables that were associated ( $p<0.2$ ) with technical success on univariate analysis.

In terms of secondary outcomes, change in PANQOLI scores, COMPAT scores, and opiate daily doses will be compared between subjects in the PPL group and ESWL group. Additional outcomes to be measured include stone recurrences and number of chronic pancreatitis-related hospitalizations during the follow-up period. Should cross-over occur, under the primary (intention-to-treat) analysis, the outcomes will be attributed to the initially randomized intervention. In the secondary (per-protocol) analysis, the outcomes will be attributed to the combination of treatments resulting in technical success. A subgroup analysis will also be performed on patients who achieved only partial stone clearance (thus considered a treatment failure) in the above-mentioned outcomes. Comparisons will be made using a chi-squared test or Fisher's exact test for categorical variables and the Student's t test for continuous variables. Paired t tests will be performed to evaluate individual changes within each arm. A p value  $<0.05$  will be considered significant.

Power analysis: A large meta-analysis by Moole et al found a complete stone clearance rate of 70% in patients who received ESWL in conjunction with ERCP.<sup>16</sup> In contrast, the largest studies examining pancreatoscopy-guided lithotripsy methods have found complete stone clearance rates ranging from 83-99%.<sup>6,14</sup> Using a conservative stone clearance rate of 90% for pancreatoscopy-guided lithotripsy, a sample size calculation was performed using a two-sided test with 80% power and significance ( $\alpha$ ) of 0.05. This demonstrated the need for 124 subjects total, with 62 in each arm. Accounting for an expected dropout rate of 20%, the sample size needed would be a total of 150, or 75 subjects in each arm.

## **2. DATA AND SAFETY MONITORING PLAN**

A Data and Safety Monitoring Board (DSMB) will be established to monitor the data and safety of this project. A DSMB will be appointed by the study team and will include at a minimum: A senior faculty member clinician with substantial research experience within the Division of Gastroenterology and Hepatology at the University of Colorado who is not involved in the study, and will serve as the group leader, a statistician, and a senior gastroenterologist from a non-participating academic institution. The DSMB will meet at least twice a year. DSMB meetings will be only open to designated DSMB staff and other individuals who have been approved to have access to unblended data. Any recommendations for alteration or termination for part or all of the trial shall be based on consideration of the accumulating data in the context of totality of evidence. Specific statistical monitoring guidelines for safety and efficacy concerning the primary and secondary endpoints will be developed in cooperation with the DSMB.

### **2.1 Definition of AEs, serious AEs, and unanticipated problems**

AEs are defined as any undesired, harmful, or pathological change in a patient as indicated by signs, symptoms, or laboratory changes that occur in association with the use of the trial interventions, whether considered intervention-related or not. This definition includes intercurrent illness or injuries, exacerbation of existing conditions, psychological events, psychosocial events, and AEs as a result of the study intervention. All endoscopic AEs will be defined and classified as recommended by the American Society for Gastrointestinal Endoscopy (ASGE).<sup>17</sup> The most common AEs for PGL are expected to include pancreatitis and bleeding. The most common infectious complications are expected to include cholangitis, cholecystitis, and less likely duodenoscope-related infection transmissions. No differences in the types and

proportion of AEs have been found in previous studies examining EHL and LL.<sup>10</sup> The risks of ESWL include post-ESWL pancreatitis, bleeding, infection, steinstrasse, and perforation with an overall AE rate of 6.7%.<sup>18</sup> Additionally, as these procedures would typically be performed as part of the management of patients with refractory PD stones at the study sites, there are no separate research risks from the risks of standard care.

The definition of a serious AE is any AE that results in any of the following outcomes: 1) death, 2) life-threatening, 3) persistent or significant disability/ incapacity, or 4) requires or prolongs hospitalization. Serious AEs are expected to include perforation, air embolism, and cardiopulmonary AEs associated with the use of general anesthesia, which will be used in all procedures.

Unexpected AEs will be defined as any AEs with specificity or severity which is not consistent with the current risk information in this investigational plan as formulated from prior studies investigating the trial interventions.

Grading of severity of AEs will be done in accordance to the grading system proposed by the ASGE and the revised Atlanta classification.<sup>17,19</sup> For pancreatitis, grading will be done according to the revised Atlanta classification as follows: 1) Mild – no organ dysfunction, 2) Moderate - transient organ failure <48 hours OR local or systemic AEs without persistent organ failure, and 3) Severe – persistent single or multi organ failure >48 hours OR present or persistent systemic inflammatory response syndrome (SIRS). All other AEs will be classified as follows: 1) Mild – AE is usually transient, does not require any special treatment, and does not interfere with the patient's daily activities, 2) Moderate – AE usually introduces a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated with simple therapeutic maneuvers, and 3) Severe – AE interrupts a patient's usual daily activity and generally requires systemic drug therapy or other intervention.

## **2.2 Procedures for documentation of adverse events**

All AEs are to be reported using the centralized online data collection system. All AEs must be entered within 14 days of occurrence. A standardized reporting system will be available on the REDCap system, which will be accessible to all study members at each site. AE reporting can be done by either site PIs or research coordinators.

All serious AEs that occur from initiation of the study to 14 days post final intervention are to be reported immediately (within 24 hours) using the electronic data collection system. All serious AEs will then be immediately relayed to the PIs. The PIs will first review the AEs to: 1) ascertain the seriousness, 2) ascertain the relationship between AE and intervention, 3) verify that all data are complete, and 4) follow-up with the specific site for incomplete data and/or data

clarification. The PIs will then submit the AEs to the DSMB, who will then review the AEs to confirm the findings of the PIs.

### **2.3 Monitoring of Data**

The DSMB will be responsible for data and safety monitoring. All primary and secondary outcomes as well as data integrity and study progress along with all AEs will be reviewed by the DSMB.

The DSMB will meet at least twice a year to review the data mentioned above. These meetings will occur in December and June for a total of at least 4 meetings during the expected 2-year study period.

An interim analysis will be performed at the halfway point of enrollment, which is expected to be at the 75<sup>th</sup> patient. Should the interim analysis reveal an unexpected accumulation of AEs or a clear superiority of one lithotripsy method over the other, the DSMB may recommend stopping the study, which will be reported to the PIs, IRB and the funding agency.

The DSMB will include at a minimum the following individuals:

- Frank Scott: Gastroenterologist, University of Colorado
- Jay Burton: Hepatologist, University of Colorado
- Biostatistician: Non-study Statistician, University of Colorado
- Sunil Sheth: Gastroenterologist, Beth Israel Deaconess Medical Center

### **3. FEASIBILITY/RECRUITMENT PLAN/MATERIALS**

The power analysis suggests that a total of 150 participants will need to be enrolled to achieve sufficient statistical power to compare the two lithotripsy methods. Based on current volume of each site performing ERP interventions, we anticipate enrollment of at least 1-2 patients at each site/month. With a total of 6 recruitment sites, we anticipate complete enrollment within 1.5 years and with a follow-up of 6 months/patient post completion of treatment, the study is anticipated to be completed within 2.5 years.

All recruitment will be done at each study site by the site-specific PI. As each study site is a referral site for patients with chronic pancreatitis who have PD stones, no advertising will be performed. All patients will be recruited based on screening done prior to regularly scheduled clinic or procedural visits.

#### 4. STAFF NEEDED

	Pre-Study Start	Screening/Eligibility	Active Study Enrollment	Study Follow-up	Study Completion
Study Primary Investigator	<ul style="list-style-type: none"> <li>•Write:               <ul style="list-style-type: none"> <li>-Protocol</li> <li>-Informed consent</li> <li>-Data and safety monitoring plan</li> <li>-Training plan</li> <li>-Budget</li> </ul> </li> <li>•Submit IRB documents</li> <li>•Create source document template, CRFs, and logs</li> <li>•Create study and subject binders</li> <li>•Create authorship/publication plan</li> <li>•Conduct in-person team/site training</li> <li>•Enter trial in <a href="http://clinicaltrials.gov">clinicaltrials.gov</a></li> </ul>	<ul style="list-style-type: none"> <li>•Identify and discuss study with potential subjects</li> <li>•Perform or review medical history and physical exam</li> <li>•Determine final eligibility based on inclusion/exclusion criteria</li> </ul>	<ul style="list-style-type: none"> <li>•Perform physical exams</li> <li>•Submit annual IRB reviews</li> <li>•Conduct monthly study conference call with study sites</li> <li>•Submit annual continuing review to funding agency</li> <li>•Review and submit adverse events to IRB/DSMB</li> <li>•Monitor study budget/payments</li> <li>•Maintain <a href="http://clinicaltrials.gov">clinicaltrials.gov</a> updates</li> </ul>	<ul style="list-style-type: none"> <li>•Review AEs reported during follow-up phone call as necessary</li> </ul>	<ul style="list-style-type: none"> <li>•Conduct close-out visits with sites</li> <li>•Notify IRB of study closure</li> <li>•Update <a href="http://clinicaltrials.gov">clinicaltrials.gov</a></li> <li>•Write manuscript</li> <li>•Disseminate published results to study participants</li> <li>•Store study records</li> </ul>
Site PI	<ul style="list-style-type: none"> <li>•Attend investigator meeting</li> <li>•Submit IRB documents</li> </ul>	<ul style="list-style-type: none"> <li>•Identify and discuss study with potential subjects</li> <li>•Perform or review medical history and physical exam</li> <li>•Determine final eligibility based on</li> </ul>	<ul style="list-style-type: none"> <li>•Perform physical exams</li> <li>•Submit annual IRB reviews</li> <li>•Participate in monthly study conference call</li> </ul>		<ul style="list-style-type: none"> <li>•Notify IRB of study closure</li> <li>•Participate in writing/review of manuscript</li> <li>•Disseminate published</li> </ul>

		inclusion/exclusion criteria	•Submit adverse events to IRB/study PI as necessary		results to study participants  •Store study records
Co-investigators	•Attend investigator meeting	•Identify and discuss study with potential subjects  •Perform or review medical history and physical exam	•Perform physical exams		•Participate in writing/review of manuscript
Study Coordinator	•Attend investigator meeting  •Assist PI/Co-PIs as appropriate	•Identify and discuss study with potential subjects  •Review medical history	•Call subject to remind him/her of visit  •Schedule study visits and procedures  •Conduct study visits  •Complete source documents	•Call subject for study follow-up phone call	•QA study database
Research Assistant	•Attend investigator meeting	•Assist PIs with above as appropriate	•Assist PIs with above as appropriate  •Enter data from source documents into REDCap		•Assist PIs with above as appropriate
Data Manager	•Create study database		•Run data integrity checks  •Create analysis datasets		•Run data integrity check  •Create analysis datasets
Statistician	•Calculate sample size  •Generate randomization lists		•Create SAS database for interim analysis		•Perform final data analysis  •Generate tables/graphs for manuscript



	•Create statistical analysis plan				
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## 5. TRAINING

	Protocol	Protocol Changes	Informed consent	Study Procedures	Data Collection Tools	Data Safety Plan	Study MOPs/SOPs	GCP	CITI training
Study Primary Investigator	X	X	X	X	X	X	X	X	X
Site Primary Investigators	X	X	X	X	X	X	X	X	X
Co-investigators	X	X	X	X	X	X	X	X	X
Study Coordinator	X	X	X	X	X	X	X	X	X
Research Assistant	X	X		X	X	X	X	X	X
DSMB	X	X		X	X	X		X	X
Data Manager	X	X		X	X	X	X	X	X
Statistician	X				X	X		X	X

### **5.1 Training Plan**

The PIs will be responsible for training all study staff. The initial training meeting will occur at the 1<sup>st</sup> Investigators Meeting involving all PIs, co-investigators, and the study coordinator. The protocol will be reviewed in its entirety and all standard procedures will be reviewed. Informed consent will also be reviewed during this session to ensure consistency across the study sites. All questions from the study staff will also be answered during this time. The protocol will then be reviewed at each site with the site-specific PIs and research assistants.

Quarterly conference calls involving all PIs, study coordinator and research assistants will be held once enrollment begins to ensure that any questions the study group has are answered. In

addition, all potential protocol changes will be discussed during these calls. Should an emergent protocol change be needed, an emergent conference call will be held to discuss the change and once agreed upon, the changes will be submitted to the respective Institutional Review Boards.

## **6. Informed Consent**

**Principal Investigator: Raj Shah**

**COMIRB No: 19-0402**

**Version Date: 2/21/19**

**Study Title: Per-Oral Pancreatotomy-guided Lithotripsy vs. Extracorporeal Shock-Wave Lithotripsy For Treating Symptomatic Main Pancreatic Duct Stones in Chronic Pancreatitis**

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You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

### **Why is this study being done?**

This study plans to learn more about what method of removing pancreatic stones is best in patients with chronic pancreatitis. We hope to compare two treatments that are both currently used to see which one is better.

You are being asked to be in this research study because you have chronic pancreatitis and you have stones in the pancreas that are hard to remove.

### **Other people in this study**

Up to 50 people from your area will participate in the study.

Up to 150 people around the country will be in the study.

### **What happens if I join this study?**

If you join the study, you will be randomly chosen for one of the two main treatments we use to remove stones in patients with your condition. You would have received one of these treatments regardless of participating in this study or not. You will be asked to complete questionnaires about your quality of life and pain levels before receiving the treatment. You will then complete the questionnaires again 1, 3, 6, and 12 months after finishing treatment.

### **What are the possible discomforts or risks?**

Discomforts you may experience while in this study include psychological harm from the questionnaires as they do ask about your personal life.

There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it can not be guaranteed.

If you become pregnant, the particular treatment or procedures involved in the study may involve risks to the embryo or fetus which are currently unclear.

### **What are the possible benefits of the study?**

This study is designed for the researcher to learn more about which method to remove stones is better. This will help researchers also understand how stone removal affects quality of life and pain”

This study is not designed to treat any illness or to improve your health. Also, there may be risks, as discussed in the section describing the discomforts or risks.

### **Are there alternative treatments?**

There may be other ways of treating your chronic pancreatitis. You may choose to get not treatment at all or you could consider surgical removal of part of your pancreas.

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

### **Who is paying for this study**

- This research is being sponsored by the American Society for Gastrointestinal Endoscopy. However, your procedures are being paid for by your insurance, as they are part of standard of care.

### **Will I be paid for being in the study?**

You will be paid \$100.00 total for your participation in this study. This stipend is meant to reimburse for your transportation fees to our hospital. You will receive a check for this amount after your 1<sup>st</sup> appointment.

It is important to know that payments for participation in a study is taxable income.

### **Will I have to pay for anything?**

It will not cost you anything to be in the study.

### **Is my participation voluntary?**

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

### **Can I be removed from this study?**

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason. Also, the sponsor may stop the study at any time.

### **What happens if I am injured or hurt during the study?**

1. We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

### **Who do I call if I have questions?**

The researcher carrying out this study is Raj Shah. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Samuel Han at 617-640-1495. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Samuel Han with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

### **Who will see my research information?**

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include

- University of Colorado Denver
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Raj Shah, 1635 Aurora Ct, Mail Stop F735, Rm. AIP 2.031

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

**Information about you that will be seen, collected, used and disclosed in this study:**

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records

**What happens to Data that are collected in this study?**

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data collected from you during this study are important to this study and to future research. If you join this study:

- The data given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data collected from you.
- If data are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

**Agreement to be in this study and use my data**

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Print Name: \_\_\_\_\_

Consent form explained by: \_\_\_\_\_ Date: \_\_\_\_\_

Print Name: \_\_\_\_\_

\_\_\_\_\_ Date \_\_\_\_\_

Print Name: \_\_\_\_\_

Witness of Signature Y

Witness of consent process Y

\_\_\_\_\_ Date \_\_\_\_\_



Legally Authorized Representative/

Proxy Decision Maker

Print Name: \_\_\_\_\_

## TIMELINE

Task Name	Dates
Complete Protocol (have protocol finished in its entirety and reviewed and agreed upon with all site PIs)	July 1st, 2019
DSMB Meeting	August 1st, 2019; December 15 <sup>th</sup> , 2019, June 15 <sup>th</sup> , 2020; December 15 <sup>th</sup> , 2020; June 1 <sup>st</sup> , 2021
1st Investigators Meeting	August 15th, 2019
Initiate Enrollment	September 30th, 2019
2nd Investigators Meeting	December 15th, 2019
Collect Data	September 30th, 2019 - Through completion of study
Interim Analysis	Upon enrollment of 75 <sup>th</sup> patient
Analyze Data and Produce Reports	December 1st, 2019; June 1 <sup>st</sup> , 2020; December 1 <sup>st</sup> , 2020; June 1 <sup>st</sup> , 2021

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